III

STOVARSOL IN THE TREATMENT OF CONGENITAL AND ACQUIRED SYPHILIS*

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ALTHOUGH nearly 20 years have elapsed since stovarsol was first recommended for the prevention and treatment of syphilis, and during that time numerous reports as to its efficacy have been published in various European countries and in the United States of America, the dearth of reports upon its use in this country is presumably *prima facie* evidence that the drug has found little favour among British venerealogists and pædiatricians.

The early history of stovarsol seems to be obscure judging by the conflicting statements one has found in the literature upon the subject. May and Baker, in their latest brochure on " Stovarsol ", state that it was " first prepared by Ehrlich but discarded by him on account of its being one of the pentavalent arsenicals, a group which he regarded as inferior to the trivalent arsenicals." Whipple and Dunham (1938), in their interesting review on congenital syphilis, state that it was first prepared by Ehrlich and Hata in 1908. Pillsbury and Perlman (1939), in a recent report on the use of acetarsone (stovarsol) in 187 cases of congenital syphilis, state that it was " originally synthesized by Ehrlich and Hata, but apparently was discarded by them as being too toxic," giving as a reference Ehrlich and Hata's monograph " Die experimentelle Chemo-therapie der Spirillose," published in 1910. I have looked through this book but have failed to find in it any reference to stovarsol. What have the British authorities to say about it ? Marshall Findlay, in the second edition of his " Recent Advances in Chemotherapy " (1939), states that " acetarsol (stovarsol) was originally studied by Ehrlich and Hata (1911), and reinvestigated by Fourneau and his colleagues (1921 and 1923)". Pakenham-Walsh (1937) simply states that

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stovarsol was discovered by Ehrlich ; he gives also a full list of its many synonyms. Paddle (1937) says " originally prepared by Ehrlich in 1909 (preparation '594'), it was discarded after trial as being too toxic." Col. Burke, in his first paper upon the subject (1925), leads one to infer that, whereas Ehrlich had prepared (but in an impure condition) the precursor of stovarsol (oxyaminophenyl arsinic acid—Ehrlich '593', Fourneau '189'), it was only in 1922, when Levaditi and his colleagues were reinvestigating these compounds with a view to finding a preparation of arsenic which would be useful as a prophylactic against syphilis when taken by mouth, that stovarsol itself was prepared, for he writes as follows: " It was decided that the addition of an acetyl group to '189' would be of value in increasing the stability, reducing the toxicity, and thereby improving the $\frac{C}{T}$ ratio.* Acetyl-oxyamino-phenyl arsinic acid, '190' or stovarsol, and its sodium salt (sodium stovarsol) were therefore prepared ".

In 1929, however, Burke writes :—" Stovarsol . . . was first prepared by Ehrlich, Benda and Bertheim (1908). It was thought by them to be oxyaminophenyl arsenious acid. The investigation was not pursued because of the toxicity of the compound and also because the arsenic in it exerts its pentavalent function. Ehrlich considered that the pentavalent arsenicals were therapeutically inferior to the trivalents, such as the arsenobenzenes. Fourneau reinvestigated the compound and prepared it in a high state of purity. He found that the toxicity noted by Ehrlich was due to impurities such as sodium arsenite. When the substance is properly synthetised it is represented by the formula given on p. 90, and is therefore acetyl-oxyamino phenyl arsinic acid ".

Finally, the obscurity in which the preparation of stovarsol is shrouded, is well brought out in the historical data given by Maxwell and Glaser in their paper which was published in 1932. They write : " Ehrlich apparently first prepared 3-amino-acetyl 4 hydroxy phenyl arsonic acid as '594' in the series of investigations that led to the discovery of '606' (arsphenamine). We have been

* " C stands for the curative dose, T for the toxic dose, C being always expressed as 1. The efficiency of these compounds varies indirectly with the size of the fraction " (Burke).

unable to find the records of Ehrlich's experiments with '594', and Raiziss (in a personal communication to the Authors) stated that no authentic account by Ehrlich concerning it exists. Bauer and Benda (1924) stated that Ehrlich discovered '594' in 1909, but that it was little used because it was overshadowed in its therapeutic effect by arsphenamine. Kolle (1924) made practically the same statement."

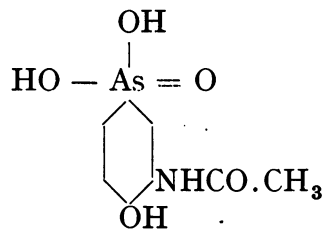
Whatever the actual facts of the origin of stovarsol may be, there is no doubt that some ten or eleven years later, Fourneau (1921) reviewing the matter came to the conclusion (1) that Ehrlich was rather obsessed with the idea of the superiority of the trivalent arsenicals over the pentavalent in the treatment of syphilis, and (2) that the toxicity of Ehrlich's pentavalent arsenicals may have been due to impurities. Tréfouël, in Fourneau's laboratory, succeeded in purifying the preparations '593' and '594' (Fourneau '189' and '190'), which were then found by Levaditi and Navarro-Martin (1922), to whom the experimental investigations were entrusted, to be less toxic than Ehrlich had originally estimated them to be. They found '189' to have a curative as well as a prophylactic value in trypanosomiasis, spirillosis of fowls and experimental syphilis in rabbits. A 10% solution of sodium stovarsol also effected a rapid cure in rabbit syphilis. The clinical assay was entrusted to Fournier, Guénot and Schwartz (1922), who found that the acid '189' acted rapidly on syphilitic lesions and destroyed the spirochætes in them. There appeared to be no drawbacks to its use and it was only feebly toxic. Later on in the same year, a further report by these investigators appeared in which the name "Stovarsol or 190" was first used. According to the Authors Stovarsol is the ideal oral prophylactic for syphilis. After it was found to be a cure for experimental syphilis in rabbits and monkeys, it was tested by Fournier and his colleagues on 80 syphilitic patients in all stages of the disease and with good results. Lastly, after it was shown to be of value in preventing experimental and sexual syphilis in *animals*, it was similarly tried and found to be successful in preventing experimental and sexual syphilis in *humans;* this applied not only to the soluble sodium salt, but *to the practically insoluble acid itself when taken by mouth.*

A good résumé of the work of Levaditi and his colleagues is given by Burke in the articles previously referred to, and although it is now several years since he drew the attention of the medical profession in this country to the value of stovarsol as a prophylactic against syphilis and for the oral treatment of infantile syphilis and certain late manifestations in acquired syphilis, it does not appear to enjoy much popularity here.

Nomenclature and Chemical Considerations of Stovarsol

There are many synonyms for the drug; stovarsol, spirocid, acetarsone, acetarsol (B.P. Addendum), orarsan (Boots), kharophen (Burroughs, Wellcome and Co.), and a number of others which will be found enumerated in Findlay's book and in Pakenham-Walsh's article previously referred to. Personally, I prefer the name STOVARSOL as being probably the most appropriate* as well as the most euphonious.

STOVARSOL is 3-Acetylamino 4-hydroxy phenyl-arsonic acid with the structural formula :—



It is prepared from 3-Amino 4-hydroxy phenyl-arsonic acid (Ehrlich '593', Fourneau '189') by acetylation. The sodium salt (stovarsol sodium) is soluble and is used for injection. Stovarsol itself is a white powder with a slightly acid taste, practically insoluble in cold water, alcohol and dilute acids. Its arsenic content is 27·2%, intermediate between that of '606', which is 32%, and '914', which is 20%. The official dose is one

* I am indebted to Col. Harrison for information as to the origin of the name "Stovarsol". The first syllable "stov" occurs also in stovaine which was likewise discovered by Fourneau. The desire to name the drug after its discoverer would have resulted in its being called "Fourneauine"—too cumbersome a name—so the English equivalent of Fourneau—"stove"—was employed and the drug given the name "stovaine", hence also "stovarsol".

to four grains (0·06 to 0·25 g.).* After oral administration it is in part excreted in the urine for Chen, Anderson and Leake (1930) found 7% of the arsenic taken in 0·5 gm. stovarsol was present in the urine after 24 hours and 20% after 72 hours (Findlay). In a case investigated by Paddle, after an oral dose of 1·25 g. (20 grs.) there was practically no increase in the arsenic content of the cerebrospinal fluid during the ensuing 24 hours (6 tests), whereas arsenic in the blood rose from 0·9 to 21·1 parts per million in 24 hours, pointing to absorption from the alimentary canal.

During the last 12 to 15 years stovarsol has been used on a considerable scale in France and even more widely in Germany for the treatment of congenital syphilis in infants and young children, and numerous reports upon its use and efficacy have been published. In the United States it has come into use since about 1930 and among the reports upon it those by Maxwell and Glaser, Pillsbury and Perlman, Rosenbaum and Traisman may be mentioned. In the review of Congenital Syphilis by Whipple and Dunham (1938) previously referred to, there is a useful résumé of stovarsol treatment in congenital syphilis and the authors remark " in spite of the fact that acetarsone (stovarsol) has been in use since 1921 and that the literature contains about 40 reports dealing with the treatment of more than 1,100 children, only *four* reports have been found in which sufficient follow-up has been made to evaluate the drug". Its apparent unpopularity in this country for the treatment of congenital syphilis is due to at least two reasons : (1) with a drug to be administered by a mother to her infant, we are entirely dependent upon the willing and intelligent co-operation of the mother and there will always be a certain element of doubt or uncertainty as to whether or no the patient is receiving its proper treatment, whereas with the weekly injection given in the clinic there is no such doubt. (2) We are rather conservative in our outlook and many of us would rather rely upon the drugs we know are of proved value—which, however, is true only if they are given in *adequate* doses—than try a remedy of which we

* May and Baker prepare and supply Stovarsol in tablets of three sizes : 10 mg., 3 cg. and 0·25 g. ($\frac{1}{6}$, $\frac{1}{2}$ gr. and 4 grains). Boots prepare and call the drug " Orarsan " and supply tablets of 10 mg., 15 mg., 3 cg., 6 cg. and 0·25 g. ($\frac{1}{6}$, $\frac{1}{4}$, $\frac{1}{2}$, 1 gr. and 4 grs.). Burroughs, Wellcome make and supply tabloids of " Kharophen " 0·25 g. ; Evans Sons, Lescher and Webb, Stovarsol 025 g.

have not heard much in this country, and of which less has been convincingly written. Such was my own feeling before 1932, so that until that time I had used stovarsol in only a few special cases; for example, where the mother and children were unable to come to the Clinic each week and the mother seemed a sensible person and likely to dose the children properly and to be able to detect any signs of incipient intoxication. Further, in a few cases where the physical and psychical trauma done to the child by each weekly injection seemed to me unjustifiable, I resorted to oral stovarsol. In Sept. 1932, I attended the Congress at Geneva of Preventive Pædiatrics and there met pædiatricians from most of the European countries, many of whom were enthusiastic in their advocacy of stovarsol or spirocid therapy and particularly the Germans, who maintained that in Germany practically no injections were then being given for the treatment of congenital syphilis. Prof. Hamburger, of Vienna, was most enthusiastic about it and told me it was in his Clinic that Dr. Bratusch-Marrain worked out his scheme of dosage which has since been adopted by many others. My main criticism at the time was that before we were in a position to maintain that stovarsol was really a *cure* for congenital syphilis, there must be adequate reports upon the ultimate clinical and serological condition of the patients, and this criticism has been borne out by the statement of Whipple and Dunham referred to above, that only four out of about forty reports give adequate details of follow-up. In working out a scheme for the testing of stovarsol, it occurred to me that if one could obtain a residential unit or colony, such as a modified Welander Home might furnish, the oral treatment of these patients could be undertaken under skilled supervision, thereby solving the difficulty of ensuring that the drug was actually being administered in the prescribed doses, and also that the onset of any toxic manifestations would be promptly noted. Through the active interest and good offices of Sir Frederick Menzies, then the Medical Officer of the London County Council, facilities for such a residential unit for congenital syphilis were provided by the Council, which unit I had the pleasure and privilege of supervising from its inception in 1933 until my retirement in 1939. We were now assured of the regularity of the treatment and of the

general care and nursing of the patients. As regards the follow-up, one had hoped that it would be possible to supervise the children before and during their school age through the Child Welfare and School Medical Services. Unfortunately, the outbreak of war disorganized the Unit and it must be left to the future to resume and fully implement the scheme, which is undoubtedly beneficent and therefore desirable. There can be no two opinions of its value to the patients—all the doctors and nurses who have worked in the Unit have remarked upon the beneficial effects upon the children of the drug, the good nursing and the improved conditions under which they live. Had the Unit been housed in the country, the results would have been even better. As the children are, or should be, in residence for at least a year, educational facilities should be provided for the older children and kindergarten for the younger ones. During the rest periods of 4 to 6 weeks between the courses of treatment, the patients should not be allowed to return home but should remain in the Unit. If allowed to go home they may become unsettled and be unwilling to return to the Unit; they may come back verminous; they never returned in as good and clean a condition as when they went home, and frequently they had lost several pounds in weight, through lack of care and attention, improper feeding and going to bed too late. The possibility of introducing infection into the Unit has also to be borne in mind.

Coming now to the kernel of this paper—the treatment of congenital syphilis by stovarsol. First, as regards dosage. Various schemes are in operation and practically all comprise rest intervals between the periods of administration of the drug. Originally 3 or 7 days' rest were allowed after a like period during which the stovarsol was given. Subsequently both the drug and rest periods were prolonged. Tuscherer (1929) started with 1 grain (6 centigrammes) daily for three days, then 2, 3, 4 and 6 grains daily for three days, 8 grains daily for 6 days and finally 12 grains (0·75 g.) daily for 20 days: total 21 g. or 336 gr. in six weeks. After a rest of 6 weeks, the course was repeated. The dosage indicated was apparently *irrespective of the age or weight of the patient*, and one can well believe that severe toxic effects were produced. Maxwell and Glaser started their observations by using

Tuscherer's dosage, but they subsequently reduced the amount given in a course to 14 g. (224 gr.) in 49 days, on account of some untoward results which occurred in their own practice and of others reported by Martin (1930).

Bratusch-Marrain (1930) was more conservative in his dosage and based it on the body-weight of the patient.

First week—5 milligrammes per kilogramme body-weight daily.
Second week—10 milligrammes per kilogramme body-weight daily.
Third week—15 milligrammes per kilogramme body-weight daily.
Six weeks (4th to 9th)—20 milligrammes per kilogramme body-weight daily.

For simplicity, I have interpreted 5, 10, 15 and 20 milligrammes as $\frac{1}{12}$, $\frac{1}{6}$, $\frac{1}{4}$ and $\frac{1}{3}$ grain respectively, and for convenience in the treatment of infants I suggested to Messrs. Boots, and May and Baker that they might supply the drug in smaller tablets than those usually marketed commercially (see p. 91). Following this scheme of dosage a patient receives about 1 gramme of the drug per kilogramme body-weight during each course of treatment, or 4 g. per kg. body-weight per annum if 4 full courses are given. I have suggested (1939) a rather more liberal dosage whereby 5·5 grammes per kilogramme body-weight are given per annum.

First week—12 milligrammes per kilogramme body-weight daily.
Second week—18 milligrammes per kilogramme body-weight daily.
Seven weeks (3rd to 9th week)—24 milligrammes per kilogramme body-weight daily.

The crushed tablets of the drug should be given suspended in water or milk half an hour before food. The whole of the daily dose should be given before breakfast or, if this is not well tolerated, it may be given in two or three portions half an hour before the principal meals. For children up to the age of 12 years I never exceed 0·5 g. a day, and for adults 0·75 g. a day is the maximum dose. If the patients are being treated as out-patients it is important that they attend once a week for observation

and to obtain their weekly supply of the drug, unless one is sure that early signs of intolerance will be detected and promptly acted upon.

After an interval of four or six weeks the course is repeated for as long as may be considered necessary, and it is here that a lack of uniformity is found. Some give one further course after the blood Wassermann reaction has become negative ; others repeat the treatment until 3 successive negative blood tests, taken one month after the conclusion of each course, have been obtained. Even then some recommend that further half-yearly courses be given for safety. Soldin and Lesser (1928 and 1930) gave as much stovarsol after the Wassermann reaction had become negative as had been given before, and this procedure was followed by Maxwell and Glaser. My own practice has been, with the adoption of the modified Bratusch-Marrain scheme of dosage given above, to allow four weeks' rest after each course which enables one to give four complete courses during the first twelve months of treatment. During this time the patient will have received about 5·5 g. of stovarsol per kg. body-weight, which may be regarded as a safe average dosage. A blood and spinal fluid test are usually carried out before the first course is begun ; the blood W.R. is repeated at the beginning of each subsequent course, and if the first test of the C.S.F. proved positive, the test is repeated every six months thereafter until a negative result is obtained. After three negative blood tests * treatment may be stopped ; if owing to sero-relapses less than three clear negatives have been recorded, the course is repeated until three successive negatives have been obtained. Thereafter 3-monthly tests for one year, 6-monthly tests the following year—with a C.S.F. test if that was originally positive—and annual blood tests for as long as may be practicable to 21 years of age or even after. In the case of older children, three or even four years' treatment with stovarsol may not result in a permanent reversal of the blood W.R. In such cases, provided the recommended

* It will be noted in the synopsis given on pp. 99–102, that many of the patients had more than three negative tests before the stovarsol or orarsan treatment was stopped. This prolongation of the treatment beyond the time that may have been necessary, was to ensure the child being kept in the Unit and under observation. If kept in the Unit without further treatment it might have been sent home by a higher authority to come up for a periodic blood test ; and if sent home there was always the possibility that it would not be brought up subsequently for the blood test.

doses of the drug have been given for at least four years and the C.S.F. is normal, one may safely disregard the positive W.R., or if desired the patient may be treated with arsenic or bismuth injections, or be given some form of pyrotherapy.

TREATMENT INTENSITY INDEX.—In the case of infants and of children up to the age of seven or eight years who have received four courses of treatment a year under the scheme of dosage outlined on p. 94, the amount of stovarsol taken, namely, 5·5 g. per kg. of body-weight per annum, may be regarded as 100 per cent. For convenience in relating treatment to other data, I have stated the weight-dosage-time factor in terms of a Treatment Intensity Index (hereafter referred to as T.I.I.). The actual amount of stovarsol will vary with the weight of the infant or child but the following are average amounts,* the figures in column 3 representing a T.I.I. of 100.

TABLE I

Age of child in years	Amount of drug taken in a course of 9 wks.	Amount of drug taken annually. Rate of :—
Half	6 grammes	24 grammes
One	8 do.	32 do.
Two	11 do.	44 do.
Three	13·5 do.	54 do.
Four	16·5 do.	66 do.
Five	19·5 do.	78 do.
Six	21·5 do.	86 do.
Seven	24 do.	96 do.
Eight	27·5 do.	110 do.

If the dosage according to body-weight were applied to unusually heavy children of nine or even eight years, their dose of stovarsol might exceed 0·5 g. daily and, as already stated, the maximum dose recommended for children up to 12 years of age is 0·5 g. From 12 to 16 years the maximum dose is from 0·5 g. to 0·7 g. and thereafter 0·75 g. daily. In other words, in the case of children 8 or more years old, the dosage is independent of the body-weight, if and when it would exceed the

* The amounts of the drug given in this table are calculated from the mean weights of children at increasing ages as given by Holt and McIntosh (Holt's "Diseases of Infancy and Childhood," 10th ed., 1936).

limits suggested for the respective ages. Table II sets out the amounts of stovarsol which it is suggested should represent a T.I.I. of 100 from nine years upwards.

TABLE II

Age of patient in years	Amount of drug taken in a course of 8 to 9 weeks	Amount of drug taken in a year
9	28·5 grammes	115 grammes
10	30 do.	120 do.
11 and 12	31·5 do.	126 do.
13	35 do.	140 do.
14	38·5 do.	154 do.
15	42 do.	168 do.
16	45 do.	180 do.
Adult	50 do.	200 do.

In the case of adults for whom the maximum annual dosage of 200 g. represents a T.I.I. of 100, the index in any particular case can be calculated from the formula $6\frac{w}{M}$, where w is the weight in grammes of the drug taken, and M the number of months during which it was taken.

MATERIAL STUDIED

This study embodies the records of 140 patients treated with stovarsol, all but about five of which were treated in the Clinic at the Hospital for Sick Children, Great Ormond Street, in the London County Council Congenital Syphilis Unit at St. Margaret's and later at St. John's Hospital, or privately by myself. The few not personally treated by me subsequently came under my care and are therefore, with the permission of the practitioners who treated them, included in this study. Of this number, Group A comprises 43 patients whose *main* treatment consisted of stovarsol or orarsan either alone or in combination with mercury—usually the protoiodide.* These are the only cases in the series which can be utilized in the evaluation of the drug for the treatment of congenital syphilis.

* In two of the cases a course of bisoxyl was given in error some time after the W.R. had been rendered negative by the stovarsol.

Group B comprising 97 patients is made up as follows :

(1) Children on stovarsol *after* other treatment . .	60	of whom 5 were under one year.
(2) Children on stovarsol *before* other treatment . .	6	of whom 3 ditto.
(3) Child with acquired syphilis (on combined treatment) .	1	
(4) Miscellaneous group (6 children of syphilitic mothers, but W.R. —, and 1 child ? syphilitic, W.R.+ and parents negative .	7	of whom 3 ditto.
(5) Mothers on combined treatment and some stovarsol .	22	of whom 4 were certainly and 2 probably congenitally syphilitic.
(6) Mother on stovarsol alone .	1	
TOTAL . . .	97	of whom 11 were under one year.

The relevant details of the patients in Group A are given in the Synopsis which follows, the abbreviations used being first set out in alphabetical order: A. = arm. æt. = aged. Arth. = arthritis. b.e. = both eyes. be. tr. st. = before treatment was stopped. Bi. = Bisoxyl (bismuth oxychloride). C. = course. C.S.F. = cerebrospinal fluid. D. = died. Di. = diarrhœa. dys. = days. Epi. = epiphysitis. F. = female. g. = grammes. Hg. = mercury. IK. = interstitial keratitis. Illeg. = illegitimate. kg. = kilogrammes. l. = left. La. sy. = latent syphilis. Li. Sp. + = liver and spleen enlarged. M = male. Ma. = marasmus. Mo. tr. b. and d. = Mother treated before and during pregnancy. Mo. tr. d. = Mother treated during the pregnancy. mth. = month. Nil. inf. = no symptoms during infancy. ON.G.C. + = gonococcal ophthalmia neonatorum. Or. = Orarsan. P. Hb. = paroxysmal hæmoglobinuria. Pe. HF. = peeling of hands and feet. Ps.-pa. = pseudoparalysis. pt. = patient. r. = right. R. = rash. Rh. = rhagades. S. = snuffles. Sa. = sulpharsphenamine. St. = Stovarsol. Te. H. and M. = Hutchinsonian incisors and Moon's molars. tr. = treated, treatment. Tx. = toxic manifestations. Vo. = vomiting. W + + = strongly positive Wassermann reaction. W + = Wassermann positive of diagnostic strength. W — = Wassermann reaction negative. W ± = Wassermann reaction

doubtful. (War) = observations discontinued on account of the war. wks. = weeks.

The 43 cases in Group A :

(1) F. æt. 1 mth. ; wt. 4·3 kg. ; Ps.-pa. l. A. ; W ++ ; 3 g. Or. in ? wks. ; W — at 7½ mths. and once afterwards at æt. 15 mths. ; Mo. unsatisfactory ; Pt. tr. at country clinic ; Tx. Vo. and R.

(2) F. æt. 1 mth. ; wt. 4 kg. ; R., S., Pe. HF. at 19 dys. ; W ++ ; Hg. 1 wk. then 20·3 g. Or. in 11 mths. ; W — at 4 mths. after 1st C., and 5 times after to 2 yrs. 11 mths. ; Tx. Nil.

(3) F. æt. 1 mth. ; wt. 2·2 kg. ; Ma., ? sy. pemphigus ; 0·58 g. Or. in 23 dys. ; W ++ at 2 and 4 wks. ; Tx. Nil. D. at 7 wks.

(4) M. æt. 2 mths. ; wt. 4 kg. ; R., S. at 6 wks., Ps.-pa. As. ; W ++ at 10 wks. ; 0·15 g. Or. in 1 wk. ; Tx. Nil. Unsatisfactory country case. D. at 12 wks. ; Broncho-pneumonia and syphilitic cirrhosis of liver.

(5) F. æt. 2 mths. ; wt. 4 kg. ; Illeg. Nil. inf. (mother W ++) ; W ++ at 10 wks. ; 1 Sa. and Bi. before 63·3 g. Or. in 8 C. in 26 mths. ; W — at 7 mths. after 10 g. Or. in 2 C., and 9 times after to 3 yrs. 3 mths., then away to be adopted ; Tx. Di. during 2nd C. on 0·78 g. a wk. ; R. during 3rd C. ; fever and poorly during 5th C.

(6) F. æt. 12 wks. ; Illeg. ; Mo. tr. d. ; No sy. and W — to æt. 10 wks., then S., R., Ma., anæmia and Li.+ ; W ++ at 10 and 12 wks. ; 1 Sa. and Hg. before Or. 4 cg. daily for 1 wk. D. at 12 wks.

(7) F. æt. 3 mths. ; wt. 5·5 kg. ; R., S., at 10 wks., X-ray pos. ; W ++ ; 38·3 g. Or. in 18 mths. ; W — at 11 mths. after 15·06 g. Or., and 6 times after to 5 yrs. 4 mths. ; 4 W — be. tr. st. ; Tx. Vo. last mth. of tr. on 0·195 g. daily. After cessation of tr. R.— papular urticaria—due to eggs and bacon, not arsenic.

(8) M. æt. 3 mths. ; Ma. only ; W ++ ; 10·85 g. St. in 2 C. in 3 mths. Tx. Nil. ; D. at 6 mths. Pneumococcal meningitis.

(9) F. æt. 3 mths. ; wt. 3 kg. ; S., Rh., Ma., Li. Sp.+, X-ray pos. ; W ++ ; 1 Sa. and Bi. before 3·75 g. Or. in 11 wks. ; W + at 5 mths. after 1 C. Tx. R. after about 7 wks'. tr. = 2·8 g. D. at 6 mths. Temp. 104° F. ? Cause.

(10) M. æt. 4 mths. ; wt. 4·5 kg. ; R., S., Ma. ; W ++ ; 5 g. Or. in 1 C. in 9 wks. ; gained 2 pounds in wt. first 4 wks. ; Tx. Nil. Removed to Ireland and defaulted there.

(11) M. æt. 5 mths. ; wt. 6·5 kg. ; R., S., Li.+ ; W ++ at 3 and 5 mths. ; 4 inf. Acetylarsan (4 m.) before 58 g. Or. in 5 C. in 16 mths. ; W — at 10 mths. after 16·95 g. Or. in 2 C., and 6 times after to 3½ yrs. ; (War) ; 4 W — be. tr. st. ; Tx. Nil.

(12) F. æt. 6 mths. ; wt. 7 kg. ; S., Li. Sp.+, X-ray pos., ulcer on buttocks ; W ++ ; 66 g. Or. in 6 C. in 18 mths. ; W — at 16 mths. after 32·92 g. Or. in 3½ C., and 4 times after to 2 yrs. 5 mths. ; (War) ; 4 W — be. tr. st. ; Tx. Di. twice in 1st C. and 1 wk. in 3rd C.

(13) M. æt. 8 mths. ; wt. 7 kg. ; ? Illeg., a foundling ; Nil. inf. ; big scalp veins ; W ++ ; 68·4 g. Or. in 6 C. in 20 mths. ; W — at 14 mths. after 14·54 g. Or. in 2 C., and 5 times after to 6 yrs. 4 mths. ; 4 W — be. tr. st. ; Tx. Nil.

(14) F. æt. 9 mths. ; wt. 8 kg. ; S., Ps.-pa., " parotitis," adenitis, dactylitis, anæmia ; W ++ ; 88·8 g. Or. in 7 C. in 20 mths. followed by Hg. ; W — at 15 mths. after 19·48 g. Or. in 2½ C., and 3 times after

to 2 yrs. 1 mth. ; (War) ; 4 W — be. tr. st. ; Tx. R. in 2nd C., Di. in 3rd C., R. in 7th C.

(15) F. æt. 10 mths. ; wt. 7 kg. ; ? Illeg., S., ON., No R. or Epi. ; W ++ ; 56·4 g. Or. in 6 C. in 21 mths. ; W — at 16 mths. after 13·89 g. Or. in 2 C., and 5 times after to 5 yrs. 1 mth. ; 5 W — be. tr. st. ; Tx. Nil. ; C.S.F. was W + and became W — in 6 wks.

(16) M. æt. 10 mths. ; wt. 10·5 kg. ; Nil. inf., La. sy., X-ray pos., inguinal hernia ; W ++ ; 62·5 g. Or. in 5 C. in 15 mths. ; W — at 19 mths. after 36·9 g. Or. in 3 C., and 5 times after to 6 yrs. 2 mths. ; (War) ; 3 W — be. tr. st. ; Tx. Nil. C.S.F. was W ±. Both parents were congenital syphilitics, the father had been treated years before at Great Ormond Street and was W —, the mother was untreated and was W ++.

(17) M. æt. 2 yrs. 1 mth. ; wt. 12·3 kg. ; S. at 6 wks. ; Arth. l. knee, sli. hydrocephalus, IK. b.e.—all at about 2 yrs. ; Te. H. and M. ; W ++ ; 147 g. Or. in 11 C. in 45 mths. ; W — at 3 yrs. 10 mths. after 85·8 g. Or. in 7 C., and 12 times after to 9½ yrs. ; (War) ; 8 W — be. tr. st. ; Tx. Nil. (Brother to Case 20.)

(18) F. æt. 2 yrs. 10 mths. ; wt. 12 kg. ; Nil. inf., IK. at 2½ yrs. ; W ++ ; 147 g. Or. in 11 C. in 46 mths. ; W — at 5 yrs. after 89·3 g. Or. in 5 C., and 6 times after to 9 yrs. 4 mths. ; (War) ; 4 W — be. tr. st. ; Tx. Nil., despite the fact that in 1st C. she had 0·5 g. daily for 5 wks.

(19) F. æt. 4 yrs. 3 mths. ; wt. 18 kg. ; Illeg. Nil. inf., Saddle nose, La. sy. ; W ++ ; 272 g. St. and Or. in 12 C. in 50 mths. ; W — at 6 yrs. 9 mths. after 157 g. St. and Or. in 8 C., and 8 times after to 10 yrs. 8 mths. ; 6 W — be. tr. st. ; Tx. Nil.

(20) F. æt. 10 yrs. ; Nil. inf., La. sy., Te. H. and M. ; W ++ ; 219·5 g. Or. in 8 C. in 36 mths. ; W — at 11 yrs. 8 mths. after 128·6 g. Or. in 5 C. and 10 times after (either W ± or W —) to 16 yrs. 5 mths. ; (War) ; 6 W ± or W — be. tr. st. ; Tx. Nil. Xerodermia better. (Sister to Case 17 ; the mother was also treated orally with orarsan and became W — in 4 yrs. 4 mths. See p. 108.)

(21) M. æt. 6 wks. ; wt. 5 kg. ; R., S., Epi. ; W ++ ; 34·6 g. Or. in 4 C. in 18 mths. with 1 C. Bi. (9·8 cc.) before the last C. Or. ; W — at 6 mths. after 8·5 g. Or. in 1½ C., and 6 times after to 1 yr. 11 mths. ; 3 W — before C. Bi. given in error ; (War) ; Tx. Nil. Remarkable improvement after 1st C.

(22) M. æt. 4½ mths. ; wt. 5·5 kg. ; S. and Eye tr. after birth, no R. or Epi., X-ray pos. ; W ++ ; 55·6 g. Or. in 5 C. in 18 mths. with 1 C. Bi. (10·8 cc.) before the last C. Or. ; W — at 14 mths. after 29 g. Or. in 3 C., and 4 times after to 2 yrs. ; 3 W — before C. Bi. given in error ; (War) ; Tx. ? Nil. ; septic sudamina after 1 mth. Or.

(23) F. æt. 2½ mths. ; wt. 3·3 kg. ; Illeg. ; Ma., no R. or S. ; W — at birth, W ++ at 2½ mths. ; 1 inj. Sa. followed by 27·8 g. Or. in 4 C. (2 with and 2 without HgI) in 1 yr. ; W — at 5 mths. after 3·7 g. Or. in 1 C., and twice after to 10½ mths. ; (War) ; Tx. Nil. A very mild infection, ? contracted at birth. Pt. removed from hospital against advice.

(24) M. æt. 14 dys. ; wt. 2·8 kg. ; S., pemphigus at 6 dys. ; W ++ at 1 wk. ; 1·14 g. Or. with Hg. in 4 wks. ; skin cleared in 2 to 3 wks. Tx. Di. after 4th wk. of tr. when taking 65 mg. daily ; Or. stopped but Di. continued till Death at 8 wks.

(25) F. æt. 8 wks.; wt. 3·4 kg.; Florid cong. syph., septic and pustular; W ++; 1 wk. Hg. alone, then in addition 16 mg. Or. daily for 1 wk.; Tx. Nil. No improvement and pt. D. at 10 wks.

(26) M. æt. 3 mths.; wt. 5 kg.; Illeg. and born in prison; ON.G.C. +, slight S., enlarged scalp veins, ? blind; W ++; 4 inf. Acetylarsan, followed by 47 cg. Or. with HgI in 11 dys. Tr. not pushed owing to infant's presumed blindness and shocking home conditions. D. at 4½ mths.

(27) F. æt. 4 mths.; wt. 5 kg.; Illeg.; Mo. tr. d. but for 14 dys. only; Nil. inf., La. sy.; Cord blood W +, child W — 3 times till 11th wk., W ++ at 15th and 23rd wks.; 1 inj. Sa. and Hg. for 4 dys. at 1 mth., then 21·36 g. Or. with HgI in 3 C. in 11 mths.; owing to war conditions blood was not tested for 8 mths. when W — at 14 mths. Tx. Nil. Is under supervision.

(28) F. æt. 4 mths.; wt. 3 kg.; Illeg.; S., Epi., developed vulvo-vaginitis G.C. + in ward at 6 mths.; W ++ at 3½ mths.; 13 g. Or. with Hg. in 2 C. in 6 mths.; W — at 8 mths. after 6·82 g. Or. in 1 C., but relapsed to W ++ at 11 mths. when G.C.F.T. was also ++, — for the 1st time. Tx. Nil. Pt. D. of whooping cough at 14 mths.

(29) M. æt. 5 mths.; wt. 6·5 kg.; R., S., Epi., Li. Sp.+; W ++; 50 g. Or. with HgI in 5 C. in 15 mths.; W — at 10½ mths. after 16·56 g. Or. in 2 C., and 5 times after to 2 yrs.; (War); 5 W — be. tr. st.; Tx. Vo. 2 dys. in 1st C.

(30) M. æt. 9½ mths.; wt. 7·5 kg.; R., S., Ma. at 4 mths.; W ++; 123 g. Or. with HgI in 9 C. in 31 mths.; W — at 2 yrs. 4 mths. after 61·7 g. Or. in 5 C., and 5 times after to 3½ yrs.; 6 W — be. tr. st.; Tx. Nil. Defaulted.

(31) M. æt. 10 mths.; wt. 8 kg.; Mo. tr. b. and d.; Nil. inf., bossed head, enlarged abdomen; W ++; 1 inj. Sa. and HgI followed by 48·7 g. Or., 0·25 g. daily, with HgI, for 6½ mths.; W — at 2 yrs.; Tx. Nil. An unsatisfactory country case. Defaulted.

(32) M. æt. 3 yrs. 7 mths.; Nil. inf.; IK. r. eye only at 3½ yrs., Te. H. and M.; W ++; 111·6 g. St. and Or. with HgI in 5 yrs.; W — at 5½ yrs. after 53·6 g. St. and 14 times after to æt. 14 yrs. 1 mth.; (War); 10 W — be. tr. st.; Tx. Nil.; C.S.F. W +, cells 20 per cmm., Lange 4332100000 at 3 yrs. 7 mths.; all normal in 6 mths. after St. 10·9 g. with HgI.

(33) F. æt. 3 yrs. 11 mths.; wt. 12 kg.; Nil. inf., La. sy.; W ++; 236 g. Or. with HgI in 13 C. in 43 mths.; W — at 6 yrs. 3 mths. after 129·8 g. Or. in 8 C., and 9 times after (either W ± or W —) to 7 yrs. 11 mths.; 7 W ± or W — be. tr. st.; Tx. Nil. Four children in this family were positive and received treatment. 2 boys, 1 older and 1 younger than pt., were negative. Parents were unco-operative and all the pts. defaulted.

(34) F. æt. 7 yrs. 7 mths.; Nil. inf., P. Hb.; W ++; 53·3 g. St. alternating with HgI during 52 wks.; 6 W ++ to æt. 9 yrs.; Tx. Nil. Pt. defaulted.

(35) M. æt. 6 yrs. 11 mths.; wt. 15 kg.; Nil. inf.; now very undersized, *fontanelle open*, Te. hypoplastic; W ++; 6·75 g. Or. with HgI in 4½ wks., Bi. later; 4 W ++ to æt. 7 yrs. 8 mths.; (War); Tx. Arsenical dermatitis, called measles; Pt. discharged home during the war.

(36) F. æt. 4 yrs. 7 mths.; wt. 17 kg.; Nil. inf., La. sy., Mongoloid;

W ++ ; 29 g. St. in 4 mths., later Bi. and two small doses Or. ; W ± at 5 yrs. 1 mth. after the St., and W — 3 mths. later after 1 C. Bi. Much Bi. tr. to æt. 7 yrs. 8 mths. ; W — 16 times to æt. 11½ yrs. ; (War) ; Tx. R. etc., see p. 108.

(37) M. æt. 6 yrs. 2 mths. ; wt. 25·5 kg. ; Nil. inf., La. sy. ; W ++ ; 25·45 g. Or. in 1 C. and 1 wk. in 2nd C., later Bi. ; W + after the Or. when R. appeared, W — at 8 yrs. after Bi. tr., and 4 times after to æt. 11 yrs. 4 mths. ; Tx. R. and trace albumen after 24 g. Or. in 8 wks. ; Pt. defaulted.

(38) F. æt. 4 mths. ; wt. 5·5 kg. ; Illeg. ; Nil. inf. ; W ++ at 2 mths. ; Sa. 0·45 g. ; W + at 4 mths. ; 0·9 g. Or. in 18 dys. ; Tx. Di. and bloodstained Vo. (? drug, ? weather). Pt. D. at 5 mths. from gastro-enteritis and pustules.

(39) M. æt. 4 mths. ; wt. 5·5 kg. ; Illeg. ; S., R. at 3 mths., X-ray pos. ; W ++ ; 6 injs. Sa. (0·15 g.) and Hg. Later 4·5 g. Or. in 21 wks. (diphtheria during this time) ; W — at 1 yr. after the Sa., Or. and 1 C. Bi., and once after at 1½ yrs. ; Tx. Circinate R., hands and feet, onychia and sores on scalp after 2·72 g. Or. in 4 wks. Pt. defaulted at 1½ yrs.

(40) F. æt. 6 mths. ; wt. 7 kg. ; Illeg. ; S. at 2 mths. ; W — at birth, W ++ at 2 mths. ; tr. 3½ mths. with Sa. (0·11 g.) and Hg. ; W — after this tr. and before 28 g. Or. in 3 C. in 9 mths. were given ; 4 more W — to 1 yr. 7 mths. ; (War) ; Tx. Vo. in 3rd C. on 20 cg. daily.

(41) M. æt. 1 yr. ; R., S. at 4 mths. ; W ++ at 4 mths. ; 2 C. Sa. (1·2 g.), then Hg. for 6 wks. ; 29 g. St. in 2 C. after which W — at 16 mths. and 2 yrs. 8 mths. W ++ relapse at 5 yrs. till 6 yrs. 4 mths., during which 58 g. St. in 4 C., alternating with Hg. and Mist. Pot. Iod., were given (all the foregoing in Canada). W + relapse again at 7 yrs. 2 mths. and recently W — 3 times to 8 yrs. 10 mths. ; total St. and Or. to date 173 g. in 11 C. during 8 yrs. ; Tx. Nil. C.S.F. negative twice—at 5 yrs. and at 6 yrs. 7 mths. Pt. still under supervision.

(42) M. æt. 1 yr. 11 mths. ; wt. 13 kg. ; Nil. inf., La. sy. ; W ++ when being tested for adoption ; 7 inj. Sa. (0·95 g.) at 1 yr. 7 mths., then 77 g. Or. in 5 C. in 16 mths. ; W — then, at 3 yrs. 2 mths., after which 1 C. Bi. (14·25 cc.) given ; 4 W — to æt. 3 yrs. 11 mths. ; (War) ; 3 W — be. tr. st. ; Tx. Di. at end of 1st C. after taking 0·25 g. daily. C.S.F. was W + at 2 yrs. and at 2 yrs. 3 mths., W — at 2 yrs. 9 mths.

(43) F. æt. 5 yrs. 6 mths. ; wt. 18·1 kg. ; Nil. inf., P. Hb. ; W ++ ; 391 g. Or. in 15 C. with HgI in 53 mths. and 1 C. Bi. (19·75 cc.), in error, after 12th C. Or. ; W — at 7 yrs. 7 mths. after 198·7 g. Or. in 8 C. Then several W ± and a W ++ at 8 yrs. 9 mths., after 4 more C. Or. ; then 1 C. Bi. and 3 C. Or. with 1 W ± and 4 W — during the 10th yr. ; Tx. ?? (" Eczema oris " at 6 yrs. after 1st C. Or. ; and pyrexia during the last C.)

Analysis of the Cases in Group A

Nos. 1 to 20 were treated with St. or Or. *alone* (no HgI) or mainly. 21 and 22 were given 1C. Bi. in error, after 3 W —. 23 was given 4 C. Or., 2 with and 2 without HgI. 24 to 34 were given St. or Or. *with HgI*. 35 to 37 had to

discontinue St. or Or. on account of toxic manifestations. 38 to 42 had an appreciable number of injections of trivalent arsenical before the St. or Or. treatment. 43 had 1 C. Bi., in error, which however seemed to make a relapsing Wassermann reaction settle down to negative.

Of the 43 patients in this group (see Table III) 31 were aged one year or under, and 12 were over one year when they came under observation. Ten of them died—all infants. Most of these were so ill that it is unlikely that any form of treatment could have saved them. Nine of

TABLE III.—SUMMARY OF RESULTS OF TREATMENT IN 43 PATIENTS IN GROUP A

Serial number in synopsis	AGE		RESULT in patients 1 yr. and under				RESULT in patients over 1 year			
	1 yr. and under	Over 1 year	W.R. became neg.	Died	Defaulted	Under supervision	W.R. became neg.	W ++	Died	Defaulted
1 to 20	16	4	10, in from 3 to 10 mths.	5	1	—	4, in from 20 to 30 mths.	—	—	—
21, 22	2	0	2, in 4½ and 9½ mths.	—	—	—	—	—	—	—
23	1	0	1, in 2½ mths.	—	—	—	—	—	—	—
24–34	8	3	4, in 5½ to 18 mths.	4	(2)	(2)	2, in 23 and 28 mths.	1	—	2. (1 W+, 1 W—)
35–37	0	3	—	—	—	—	—	3	—	—
38–42	4	1	3; 1 after relapses; (1 was neg. at the start).	1	(1, W—)	—	1, after 15 mths. C.S.F. also became neg.	—	—	—
43	0	1	—	—	—	—	1, in 25 mths. then relapsed.	—	—	—
TOTALS	31	12	20	10	1	—	8	4	0	0

Of 31 patients aged 1 year and under, 10 died and 1 had a negative W.R. at the start of the stovarsol treatment, leaving 20, of whom 19 became W.R. negative; 1 defaulted.

Of 12 patients over 1 year, 8 became negative, 1 defaulted and 3 had to discontinue stovarsol treatment on account of toxic symptoms; 2 of these later became negative after bisoxyl injections, and 1 is still under observation.

the ten were less than six months old when they died, and in every case the W.R. was still positive. The tenth patient died at 14 months of whooping cough, the W.R.

having become negative at 8 months after one course of stovarsol, but relapsed 3 months later after a second course. Of the 33 patients who survived, no fewer than 25 showed a direct serological reversal to negative; two became negative but, after several slight relapses, were negative when last tested at nearly nine and ten years respectively; one had a negative W.R. when the stovarsol treatment was begun, 2 defaulted with the W.R. still positive, and 3 who developed skin reactions, had to give up stovarsol treatment with the W.R. still somewhat positive; so that *of the 32 patients with positive W.R. who were treated with stovarsol, no fewer than 27 or 84 per cent. became W.R. negative.*

The amount of time and treatment required to bring about serological reversal varied from one course of 2½ months, during which 3·7 g. stovarsol were given to an infant of 2½ months (case 23), to 8 courses in 2½ years, during which 157 g. stovarsol were given to a girl of 4 years 3 months (case 19). She took in all 272 g. of orarsan in 12 courses in 50 months without showing any signs of intolerance. Nine blood tests were negative from 6 years 9 months to 10 years 8 months. Another girl aged 5½ years (case 43), took 25 months, during which 198·7 g. of orarsan in 8 courses with the protoiodide of mercury were taken, to become W.R. negative. During the succeeding 14 months there were several slight relapses in the W.R. and eventually a strong positive at 8 years 9 months although an additional 108 g. orarsan had been taken in 4 courses. A course of bisoxyl, given in error, rendered the W.R. negative, and after 3 more courses of orarsan (84 g.) there were one doubtful and four negative tests between the ages of 9 years 1 month and 9 years 11 months. The total amount of orarsan taken during 4 years and 5 months was 391 g. with a T.I.I. of 86. The only possible signs of intolerance were (1) dry eczema of the face—the "eczema oris" of Leonard Findlay—at the age of 6 years after the 1st course of orarsan, and (2) a continued pyrexia during the last course at the age of 9 years. On stopping the drug the fever abated.

As one would expect, the younger the patient when treatment is begun the shorter will be the time required to convert a positive W.R. into a negative. In the case of the children under 1 year, the shortest times were 2½ and 3 months ranging up to 9½, 10 and in one case to

18 months. In the older patients the shortest time was 15 months in a boy just under 2, then 20 months in a girl of 10, 21 months in a boy of 2 years 1 month (the last two were siblings), 23, 25, 26, 28, and 30 months in children aged respectively 3 years 2 months, 5½ years, 2 years 10 months, 3 years 11 months, and 4 years 3 months.

In the case of infants the W.R. has remained negative for from one year to six years and four months, with from one to ten negative tests; in the case of the older children, the W.R. has remained "more or less negative"* from 5½ years to 16 years 5 months, with from 7 to 15 negative tests.

The Effects of Stovarsol Treatment

Practically all who have used stovarsol in the treatment of congenital syphilis are agreed upon its curative value and particularly upon the beneficial effect it has upon the child's general condition. A florid rash may show marked improvement at the end of a week, and have completely cleared in 14 to 21 days. It may take from 3 to 5 days for the spirochætes to disappear from the cutaneous lesions, so that stovarsol is definitely slower in its action on spirochætes than is arsphenamine, and no more rapid than some bismuth salts. Repeated X-ray examination of the limbs shows that the lesions of osteochondritis, epiphysitis, etc., have usually disappeared after one course of treatment. As a rule the infants make good progress, rapidly put on weight and are happy and contented. It is obvious that the bogey of the weekly injection plays upon the minds of some children, when one compares the temperament of those on oral stovarsol and those on injections of arsphenamine or bismuth.

Even a positive cerebrospinal fluid can be reversed by stovarsol treatment. A child of two years (No. 41) became negative in 9 months after 3½ courses of orarsan (48·7 g.) together with mercury iodide gr. $\frac{1}{6}$ b.d. Another child (No. 32), three and a half years old, became negative in six months after 10·9 g. stovarsol alone. In each case the blood was not negative till some months later.

* By "more or less negative" one means that some of them have shown slight serological relapses, W ± on one, two or more occasions—possibly the so-called "non-specific positives".

Toxic Effects of Stovarsol

Before stovarsol was used in the treatment of congenital syphilis, it had already been used in other diseases : amœbiasis (Marchoux 1924, Brown 1935), acquired syphilis, yaws, trypanosomiasis and malaria (Levaditi 1925), and a formidable list of toxic manifestations can be compiled from the literature. Bender (1927) recorded six cases of poisoning with malaise, fever, œdema, jaundice, diarrhœa, albuminuria, bronchitis, coryza and skin troubles, such as diffuse erythema, dryness and pruritus. Of 232 cases of amœbiasis treated by Brown (1935) without a death, thirteen (5·6%) had toxic erythemata, some of them so severe as to amount to exfoliative dermatitis (G. M. Findlay).

Paddle treated a group of 29 congenital syphilitic mental defectives, ranging from 11 to 59 years of age, with stovarsol following in the main Bratusch-Marrain's dosage. As many as 13 of the 29 developed toxic symptoms at some time or another. These were erythematous rashes (6), herpes (3), pharyngitis (3), enlarged cervical glands, vomiting, drowsiness (2 each), and 1 case each of stomatitis, aplastic anæmia in a woman of 61 (fatal), congestion of the lung, dysphagia and collapse. He too found the skin rashes the most troublesome of all the complications ; 6 out of 18 or one-third of the females were thus affected, and none of the males. In the early stages in troublesome cases intravenous injections of calcium thiosulphate 0·6 g. in 5 c.c. sterile water were found effective. All his cases developed eosinophilia, but its degree bore no relation to toxic reactions and it could not be relied upon as an indication of intolerance.

The toxic effects in children are much less varied than in adults, and according to Maxwell and Glaser they are much less common in infants than in older children. My own experience does not coincide with theirs, for of my 117 juvenile patients, 41 were under one year and 76 were over one year when the stovarsol treatment was started. The 41 infants furnished 14 (possibly 15) toxic cases, *i.e.*, 34 (possibly 36·5) per cent., against 11 (possibly 15), *i.e.*, 14·4 (possibly 19·7) per cent. amongst the 76 older patients. Among the doubtful or " possible " reactions were (1) septic sudamina after one month's stovarsol treatment, (2) a rash four months after cessation of treatment diagnosed by a dermatologist as " scabies

and impetigo, with now few relics of the latter with sulphur dermatitis " ; (3) a case of " herpes labialis et ani " which occurred in a girl of 4 years 7 months, five to six weeks after the termination of the third course of orarsan ; (4) a cloud of albumen in the urine two months after the cessation of a course of orarsan ; (5) repeated febrile attacks in a child who often had albuminuria during antecedent treatment with bisoxyl and who had septic tonsils ; and (6) the " eczema oris " and pyrexial attacks in case 43 already referred to.

My own view is that the skin lesions were probably due to the drug even though they might not conform to the usual appearances of arsenical erythema or dermatitis. The interesting microchemical studies made by Osborne (1928) on the deposition of arsenic in the skin in arsenical dermatitis, showed that pentavalent arsenic has a special affinity for ectodermal structures, *e.g.*, the epidermis, papillæ, hairs and hair follicles, the sweat and sebaceous glands, with relatively less affinity for the blood vessels in the corium. The trivalent arsenicals, on the other hand, have a special affinity for the vascular structures, *e.g.*, the small arterioles and capillaries below the papillæ. It is probable that the arsenic, which may be profusely deposited in the skin during the administration of stovarsol, acts as an irritant in predisposed individuals and may produce lesions of papular urticaria, eczema, etc., which, although not typical of arsenical poisoning, are none the less caused by the relative overdosing with arsenic and should therefore be regarded as danger signals.

A similar doubt exists as to the cause of an attack of vomiting or diarrhœa or both, especially in an infant. This *may* be due to the arsenic, on the other hand it often occurs, especially during the summer months, when arsenic as the causal agent is out of the question. The toxic manifestations in children under 1 year included diarrhœa (5), rashes (7), vomiting (3), onychia (1), fever (1) ; some patients exhibited more than one symptom. Fourteen of the 41 patients who were under 1 year when they came under observation died ; 4 from causes unrelated to their syphilis, 7 from the severity of their syphilis or their poor condition on admission, and three *possibly* from the stovarsol treatment, though I believe not, as the drug had been stopped and the diarrhœa and

vomiting were uncontrollable. Among the children over 1 year, there were vomiting (2), diarrhœa (2), irritation of the vulva with scratching (1), complaint of a " feeling of pins and needles all over after taking the drug " by a girl with early tabes (1), nausea, abdominal pain and vomiting (1), and dermatitis (3).

These skin cases were rather interesting. The first (no. 35 in the Synopsis) was that of a very underdeveloped boy of 7 years, who weighed only 15 kg. and who was treated with orarsan according to his body weight and was given in addition mercury iodide gr. $\frac{1}{8}$ b.d. During the fifth week of treatment, after he had taken 6·75 g. of orarsan, he developed a dermatitis which apparently so closely resembled measles that the patient was forthwith despatched to the fever hospital as a case of measles. He had no catarrhal symptoms or Koplik's spots and should have been recognized as being almost certainly a case of arsenical dermatitis. On the other hand, it is stated that coryza and even Koplik's spots may occur in arsenical dermatitis, which would certainly add to the difficulty of making a diagnosis. In this case the rash cleared in a week after the orarsan was stopped, and the patient was returned from the fever hospital to the Unit.

The second skin case (no. 36) was a girl of 4 years and a half with latent syphilis who, after four months' treatment during which she had taken 29 g. of stovarsol, developed a rash, impetigo and slight albuminuria ; these all cleared up in six weeks on withholding the drug. On resuming the treatment, a single dose of 0·1 g. brought back all the impetigo. She was then given injections of bismuth which agreed with her for a time, but she relapsed later on two occasions. Some two years afterwards orarsan was tried and two doses (0·2 g.) brought the rash back again. At the age of 11 years 5 months she was somewhat rashly given a provocative injection of 0·3 g. neoarsphenamine, which was rapidly followed by a widespread rash in the groin so that the child was in a terrible condition when she was brought to the clinic the following week. The dermatologist who saw her said it was not an arsenic rash but due to pus cocci. The latter part of the diagnosis was no doubt correct, but one cannot help feeling that the arsenic injection precipitated the dermatitis in an allergic subject. There may be a familial susceptibility to arsenic in this case, for this patient's sister was referred to on p. 107 (case 3) as having developed " herpes labialis et ani " $5\frac{1}{2}$ weeks after a course of orarsan. The third skin case (no. 37) was that of a boy, aged six years two months, with latent syphilis, who developed an arsenical rash and a trace of albumen in the urine after one course of orarsan (25·45 g. in eight weeks) and 1·36 g. one month later, on starting a second course. On withholding the drug the rash disappeared in 23 days and the W.R. was still very strongly positive. After three courses of bisoxyl (29 injections = 50 cc.) his W.R. was negative at 8 years and he had five negative tests to 11 years 11 months.

Among the other cases which may be individually mentioned are :— No. 5, which showed probably three different manifestations of overdosage ; diarrhœa during the second course when taking 0·1 g. a day ; a rash during the third course ; and a temperature with a general

run-down condition during the fifth course. No. 7 developed sickness at 20 months on 0·2 g. a day during the last month of treatment. Four months after the treatment ceased the child was brought up on account of a rash which proved to be a papular urticaria brought on by her being given bacon and egg for breakfast, for it disappeared permanently when bacon was omitted from the dietary. No. 14 had a rash during the second course, diarrhœa during the third course and a rash in the 7th course; on each occasion relief was obtained by stopping the treatment for a few days to a week. This infant's mother also developed diarrhœa after orarsan, as well as after mercury iodide. No. 18, at the age of three years (wt. 12 kg.), received 0·5 g. orarsan a day for five weeks during the first course, instead of 0·25 g. daily according to the Bratusch-Marrain scale of dosage, yet she showed no toxic symptoms. Nos. 17 and 20 were brother and sister who lived in the country so that the mother was unable to bring them to the clinic once a week for injections. They were therefore all treated orally with orarsan. The mother took 407 g. in 12 courses during 45 months (T.I.I. 54·3); her W.R. reversed from strong positive to negative in 4 years and 4 months and she had four negative annual tests from 1936 to 1939. The girl, 10 years old, received 219·5 g. orarsan in 8 courses during 36 months (T.I.I. 52); her W.R. became negative in 20 months after 5 courses (128·6 g.) and she has had 11 "more or less negative" tests to the age of 16 years 5 months, the last 4 being quite negative. The boy, aged 2 years, received 147·2 g. orarsan in 11 courses during 45 months (T.I.I. 65·9); his W.R. became negative in 21 months after 7 courses (85·8 g.) and he has had 13 negative tests to the age of 9½ years. Notwithstanding the considerable doses of the drug which were given to these patients and the duration of the treatment, none of them showed the slightest sign of intolerance, but on the contrary, they all did extremely well, and the girl who suffered from xerodermia derived much local benefit.

No. 28 had a double infection, syphilitic and gonococcal. The W.R. which was strongly positive at 3½ months was reversed to negative at 8 months after one course (6·8 g.) of orarsan, when the gonococcus complement fixation test was also negative. At 11 months, after a second course of orarsan (5·9 g.) the W.R. had relapsed and the G.C.F.T. had become positive. She then started on a third course of orarsan but developed whooping cough to which she succumbed at the age of 14 months.

Most of the complications encountered have been mild and were met by withholding the drug for a few days to a week or more. In the case of rashes it is advisable to proceed cautiously if the drug is tried again, and in a severe case it is wisest to switch over to another form of treatment. That some observers have noted many more complications of stovarsol treatment than have others, may be due to the fact that different brands of the drug may vary slightly in their composition, especially as regards their ultimate purity. I have not come across any cases of flaccid paralysis after stovarsol, such as have

been described by Martin and Maxwell and Glaser. These were undoubtedly due to overdosage—Martin's dose being no less than 0·75 g. a day even for infants! One has however seen a few such cases in children who had been overdosed with arsphenamine, *e.g.*, six weekly injections of sulphostab 0·5 g. to a child of 3½ years.

Coming now to the 97 cases in Group B (see p. 113), although these constitute more than two-thirds of the total number of patients under review, they cannot be used to assess the value of stovarsol in the treatment or prevention of syphilis, for in this group stovarsol was merely an incident in the treatment and not its main or only component. The cases may be reviewed however from the point of view of toxic reactions, and some of the cases which present points of interest will be individually referred to.

The 97 cases in the group comprise 74 children, of whom 11 were under one year, and 23 mothers, of whom four were certainly, and two others probably, congenital syphilitics. Among the 74 children, 10 (possibly 14) showed toxic symptoms, the 11 infants in this group accounting for three—rash (1), vomiting (2). The 63 older children accounted for only 7 (possibly 11) toxic reactions, which however may be largely due to the fact that a number of them had received only one to three months' treatment with the drug.

Of the 23 mothers treated, six developed signs of intolerance; one had a very bad arsenical dermatitis after having taken 0·75 g. daily for a fortnight and not having stopped the treatment as soon as the rash appeared. It is of interest to note that this patient's baby also had a rash after stovarsol—a second instance of familial idiosyncrasy. Another mother developed an eczematous rash and swelling of the ankles after having taken 211 g. in 26 months (T.I.I. 48·7). A third mother also had a rash after 3 months' orarsan treatment, but she was able to resume treatment after a rest of three months. This patient stated that she could not tolerate the drug during the menstrual period as it made the flow too profuse. Another mother developed diarrhœa, a fifth said it did not agree with her, producing gastro-intestinal upset, and the sixth developed albuminuria during pregnancy. It was given to six mothers during pregnancy without ill effects and with benefit to them-

selves and their offspring—all the babies subsequently seen (4) had negative Wassermann reactions.

The commonest, as well as the most troublesome, complications were the skin reactions, as has been noted by Paddle and others. The figures in the present series of 140 cases work out as follows : 18 rashes were directly, and probably 10 more indirectly, due to the arsenic ; of these, 8 (4 direct and 4 indirect) occurred amongst the 51 male patients—an incidence of 16 per cent. ; whereas 20 (14 direct and 6 indirect) occurred amongst the 89 female patients (22·5 per cent.). The 89 female patients included 23 mothers, of whom only three (13 per cent.) developed skin reactions. These numbers differ markedly from those recorded by Paddle, who found that none of his males, but six of his 18 females, were affected dermally.

The following cases in Group B are of interest. Stovarsol or orarsan was given in four cases of relapsing interstitial keratitis (I.K.) :

(1) In a youth of 16, ten years after the original attack of I.K. the W.R. having been negative (but Kahn positive) for five years. He took 42·3 g. orarsan in three months with benefit and without toxic manifestations (T.I.I. 94).

(2) A lad of 11 years one month had a very acute flare up of I.K. while actually under treatment with bisoxyl and Bayer '914.' On this occasion the right eye was affected, whereas at the first attack of I.K., 21 months previously, the left eye was alone, and severely, affected. The W.R. had been negative for about six months when the I.K. relapsed and it was subsequently negative on nine consecutive occasions to the age of 16 years 10 months. He received 58·2 g. orarsan in six months without reaction (T.I.I. 80·6).

(3) A girl, aged 12 years one month, developed a mild I.K. in the left eye after four years with a negative W.R.—but Kahn positive—reaction in the blood. Seven years previously she had had I.K. and iritis in the right eye only, for which she was given 52 injections (86 cc.) of Muthanol. (This is stated to be " Bismuth hydroxide in olive oil with $\frac{1}{10}$ microgram radioactivity ".) For the second attack of I.K. she was given orarsan by mouth, 96·8 g. in 16 months (T.I.I. 48·4). There were no ill effects and by that time the eye had apparently completely recovered. Six months later, however, the patient attended with a retinal hæmorrhage in the left eye, for which she is still under treatment. The blood has given 13 " more or less negative " tests between the ages of $7\frac{1}{2}$ and 19 years.

(4) A girl who, at the age of 11 years 5 months, had a relapse of I.K. in the left eye. The previous history was as follows : Only slight symptoms in infancy ;—snuffles lasting one month and a " teething " rash. At $9\frac{1}{2}$ years the knees were swollen and painful and diagnosed as rheumatic fever. At 10 years 2 months the patient developed I.K. in the right eye, and two months later in the left eye. For this she was treated with injections of bisoxyl, but on account of toxic

symptoms (stomatitis and a blue line in the gums), sulfarsenol was substituted for the bismuth. As the patient was sick after 0·3 g. sulfarsenol, the injections were discontinued and orarsan given by mouth. She took 174·5 g. during 14 months over a period of 25 months, without toxic symptoms (T.I.I. 57). The W.R. was never quite negative to age 15 years one month, when the patient defaulted.

In addition to the foregoing instance of tolerance for pentavalent arsenic when the trivalent disagreed, is the following. A small boy, aged 2 years 9 months, had an immediate generalized erythema lasting about an hour, after an injection of 0·1 g. sulphostab. The mother had previously also reacted to an injection of 0·45 g. N.A.B. with headache, dizziness and being ill for a week, so that both mother and child were treated with bisoxyl. As the boy developed a rather severe bismuth albuminuria, the injections were stopped and orarsan given orally, of which he took 97 g. in 5 courses in 18 months, without ill effects (T.I.I. 100). He * was subsequently given two further courses of bisoxyl and a final course of sulpharsphenamine, the first two injections of which gave rise to immediate reactions: pallor, vomiting and feeble pulse, which it was suggested might have been psychical in origin.

Two children had streptococcal infections, one of the kidneys (with hæmaturia and later albuminuria alone) and of the cervical glands; the other of the tonsils and cervical glands with albuminuria after bismuth injections. The former, aged 4 years 2 months, took 21·5 g. stovarsol in two months, together with mercury iodide, without ill effects (T.I.I. about 125). The latter, aged 3 years 4 months, was given 81·8 g. orarsan with mercury iodide in 17 months (T.I.I. 88) during which period he had several febrile attacks (102–103° F.). These were probably due to the septic tonsils, for they did not recur after the tonsils were enucleated towards the end of the period of orarsan treatment.

An infant, one month old, had 24 injections of bisoxyl (12·2 cc.) in 8 months, during the whole of which time it was breast-fed and the mother was being treated with N.A.B. and protoiodide of mercury pills. The child's W.R. and Kahn were negative at 11 and 12 months, but although 5 injections of sulphostab (0·425 g.) and oral protoiodide of mercury were then given, the W.R. and Kahn relapsed to strong positive at the age of 18 months. Oral orarsan 77·275 g. and a little protoiodide (2 months) given during 12 months out of a possible 16 months (T.I.I. 132) reversed the W.R. and Kahn reaction so that there were nine negatives to the age of 5 years 10 months.

Two further cases of heavy dosage may be mentioned: a child, aged 1 year 7 months, was given 15 injections of sulphostab which had rendered the W.R. negative, but he cried so much at each injection that it was deemed advisable to give stovarsol orally to complete his cure. At 2 years of age he was given 18·63 g. in six months, of which 14 g. were given in 3 months (T.I.I. 127); and during the last two weeks of the course he took 0·5 g. a day without toxic manifestations. There was one subsequent negative W.R., after which the patient was unfortunately lost sight of.

* He had by this time passed out of my care owing to my retirement from the service of the London County Council.

The second case was a child who was first seen at the age of 11 months when his W.R. was found to be strongly positive. After a year's treatment (32 injections sulfarsenol = 3·57 g.) four negative blood tests were recorded during a period of 15 months. He then defaulted at 3 years of age. Five years later he was brought back to the clinic on account of tenderness of hands and feet, which was found to be due to syphilitic periostitis, and giving a history of interstitial keratitis two years previously. The W.R. had relapsed to strong positive and it was still fairly strong after a further 2 years' treatment with arsenicals, during which 47 doses, (2 N.A.B. = 0·45 g., 45 sulphostab = 14·9 g.), were injected. At the age of 10 years 10 months stovarsol treatment was begun and during a period of five years he took 274 g., the usual dose being 0·5 g. a day. During one eight months' period he took 80 g. with no ill effects (T.I.I. 75), but on the other hand the W.R. was never quite negative to the age of 16 years 2 months, after which the patient defaulted.

In this group of cases the effect on the W.R. was not nearly so striking as in the group A cases and for the reason already given,—that the stovarsol was usually an *incident* in the treatment and not the most important part thereof. The results were briefly as follows :—

(*a*) W.R. reversed from + + or + to negative in 13 cases (including 3 mothers, one of them congenital). Five patients had adequate treatment (T.I.I. 50 or higher), three had inadequate treatment, four had combined treatment (including 1 juvenile, acquired case) and 1 mother developed dermatitis early in the treatment but had a negative W.R. after $6\frac{1}{2}$ and $13\frac{1}{2}$ months.

(*b*) W.R. reduced in 7 cases,—5 children, of whom 2 only had adequate treatment, and two mothers, neither of whom had adequate treatment.

(*c*) W.R. unchanged in 27 cases,—20 children, of whom only 4 had adequate treatment, and 7 mothers (2 congenital, 2 probably congenital), of whom 5 had adequate treatment.

(*d*) W.R. became stronger in 4 cases,—3 children and 1 mother.

(*e*) Three patients did not persevere with the treatment owing to its disagreeing with them,—2 children and 1 congenital mother.

(*f*) Three patients defaulted after the stovarsol treatment.

(*g*) Forty patients,—32 children and 8 mothers,—had negative Wassermann reactions when the stovarsol treatment was started.

If we omit the 17 mothers and 1 child with acquired

syphilis we are left with 79 cases of congenital syphilis (including 6 mothers) with the following results :—

(*a*)	W.R. reversed, including one congenital mother	in 10 cases.
(*b*)	W.R. reduced, 2 after full treatment .	in 5 ,,
(*c*)	W.R. unchanged, 20 children and 4 mothers (2 certainly and 2 probably congenital syphilitic) . . .	in 24 ,,
(*d*)	W.R. stronger	in 3 ,,
(*e*)	Treatment discontinued by 2 children and 1 mother	in 3 ,,
(*f*)	Defaulted	in 2 ,,
(*g*)	W.R. negative at the beginning of stovarsol treatment	in 32 ,,

from which it follows that of the 47 cases of congenital syphilis with positive W.R. treated with stovarsol, in addition to other drugs,
10 only were reversed to negative,
5 were reduced in intensity,
3 became stronger,
5 discontinued treatment, and
24—just half—were unchanged, though it must be noted that most of them had insufficient treatment upon which to base any conclusion.

Summary

1. The history of the preparation and therapeutic essay of Stovarsol is given.

2. Its synonyms and chemical structure. The original name, Stovarsol, preferred to any of the synonyms.

3. Value of stovarsol in the oral treatment of congenital (and acquired) syphilis. Paucity of English reports and the inadequacy of most of the reports hitherto published, upon its use.

4. Conditions under which alone it should be given. Modified "Welander Homes" recommended as Congenital Syphilis Units for the residential treatment of patients suffering from this disease.

5. Review of schemes of dosage that have been employed. Scheme of dosage suggested for children (based on that of Bratusch-Marrain) and for adults. "Treatment Intensity Index." When to suspend treatment: final tests.

6. Records are given of 140 patients treated with stovarsol. In 43 of these, stovarsol formed the main element of the treatment. Ten died, 9 at under six months from the severity of their infection, and 1 at 14 months of whooping cough. Twenty-seven out of 32 patients (84 per cent.) became W.R. negative on the treatment.

7. The effects of stovarsol treatment are given: the curative, tonic and beneficent; also the toxic manifestations, which comprise mainly rashes, but also gastro-intestinal upsets—vomiting and diarrhœa. Urinary reactions have been very rare and those referable to the nervous system, absent. It is suggested that some of the skin lesions may be indirectly due to the arsenic administration, even though primarily due to another cause, *e.g.*, cocci, dietetic (allergic).

8. A number of cases with toxic manifestations and other features of interest are given in some detail, among them two instances of familial idiosyncrasy.

9. Among the 23 mothers treated were 6 congenital syphilitics (4 certain and 2 probable), and 5 expectant mothers. There were six cases of intolerance, but only 1 (albuminuria) in a pregnant mother. The babies examined, 4 in number, were healthy when seen.

10. In 96 of the 97 cases in group B, stovarsol formed only a subsidiary part of the treatment. Of the 47 cases of congenital syphilis with positive W.R. in this group only 10 became negative, 5 became weaker, 3 stronger, 24 were unchanged and 5 discontinued treatment.

Conclusions

1. We have in stovarsol a valuable drug for the easy and oral treatment of congenital syphilis, provided it can be given under suitably controlled conditions.

2. Given in the moderate dosage indicated in the paper, there is little risk of any serious mishaps provided the early signs of intolerance are recognized and the administration of the drug stopped.

3. The results appear to be quite as good as those obtained with injections of the arsphenamines. As we do with arsphenamine treatment so we should do with oral stovarsol,—combine it with mercury, either by mouth or by inunction; *injections* of mercury or bismuth would

do away with the great advantage of *oral* stovarsol treatment.

4. Time will show whether the cure is permanent or not.

5. It has not been tried in cases with a heavily infected cerebrospinal fluid with a paretic type of Lange curve, and until this has been done one cannot express an opinion as to its value in such cases.

6. It can also be used for the prevention of congenital syphilis by its administration to expectant mothers.

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